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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/[illegible]41	[illegible]/97	SCHREIBER, S	

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EXAMINER	
BECKER, A	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 08/922,240	Applicant(s) Schreiber et al.
	Examiner Anne Marie S. Beckerleg	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-36 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-36 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

The disclosure is objected to because of the following informality: on page 56, line 9, the example is numbered, "Example 3"; however, example 2 is missing, and on page 58, line 27, there is a second "Example 3". Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting calcineurin/NF-AT mediated transcription *in vitro* using a combination of mutated cyclophilin or FK506 binding protein and mutated cyclosporin A or FK506 respectively, does not reasonably provide enablement for methods of inhibiting calcineurin/NF-AT mediated transcription *in vivo,* for methods of inhibiting proliferation of hematopoietic cells *in vivo* or *in vitro,* or for treating graft-versus-host disease in a patient using any mutated macrolide/macrolide binding protein combination. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification discloses the synthesis of macrolide analogs and altered macrolide binding proteins (MBP) with compensatory mutations that allow the mutated MBP and macrolide to bind each to the other but not to their wild type counterparts, while at the same time retaining the ability of the complex to interact with a third wild type binding partner resulting in inhibition of calcineurin/NF-AT mediated transcription. The specification discloses that in a preferred embodiment of the invention, the macrolide can be an analog of cyclosporin, or FK506, and the mutated MBP can be cyclophilin or FKBP. The applicant further discloses that a DNA encoding a mutated MBP can be inserted into a cell, preferably a hematopoietic cell, resulting in selective sensitivity to a complementary macrolide analog. The ultimate purpose of the invention is the prevention or treatment of graft-versus-host disease, or the treatment of autoimmune disease by targeting the expression of the mutated MBP to T cells *in vivo* wherein exposure of the animal to the macrolide analog would selectively prevent activation of the T cells expressing the mutated protein. The specification also provides several *in vitro* working examples demonstrating the generation of complementary pairs of altered macrolide/macrolide binding proteins that are capable of binding to wild type calcineurin and inhibiting NF-AT mediated transcription.

The specification does not provide an enabling disclosure for inhibiting proliferation of hematopoietic cells *in vitro* or *in vivo*. The applicant's working examples disclose *in vitro* transcription assays which utilize transformed human T cells (Jurkat cells) transfected with an expression vector encoding a mutated MBP, wherein exposure of the transfected cells with a complementary macrolide analog results in inhibition of NF-AT dependent transcription; however,

the specification does not demonstrate a correlation between the inhibition of transcription observed in cells stimulated with phorbol ester and ionomycin and inhibition of cellular proliferation caused by any and all growth factors. Mori et al. teaches that while FK506 can inhibit IL-5 synthesis in response to IL-2, it does not inhibit IL-2 mediated proliferation of T cell clones (Mori et al. (1997) J. Immunol., Vol. 158, page 3661, column 2, lines 3-12, and page 3662, Figure 2b). Further, the specification does not provide guidance as to the level of transcriptional inhibition necessary to inhibit proliferation. The application's working example which does utilize an *in vitro* proliferation assay only demonstrates that the cyclosporin analog CsA^{t-} fails to inhibit proliferation in cells expressing endogenous wild type cyclophilin and calcineurin. In addition, while the specification's transcriptional assays demonstrate the concentration of macrolide analog required to achieve 50% or greater inhibition of transcription in cells expressing an unknown level of mutated MBP, they do not provide guidance as to the level of mutated MBP expression required for the successful inhibition of transcription or proliferation.

Successful inhibition of proliferation using the instant invention is complicated *in vivo* by the need to selectively transfect or transduce hematopoietic cells in a multicellular environment. The specification discloses that many expression vectors may be used for this purpose, including plasmid vectors and viral vectors. The specification also discloses that methods were available at the time of filing to selectively target specific vector constructs to hematopoietic stem cells or hematopoietic cells. However, the prior art does not teach the selective targeting of vectors to hematopoietic cells *in vivo*; Schwarzenberger et al. and U.S. Patent No. 5,166,320 referenced on

page 30, lines 17-18 of the specification do not disclose the *in vivo* use of the c-kit gene delivery system. Furthermore, those skilled in the art at the time of filing did not consider the targeting of vectors to specific cell types for gene therapy to be predictable *in vivo.* Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). Thus, in the absence of evidence to the contrary, in view of the lack of guidance in the specification as to the level of expression of a mutated macrolide required to inhibit transcription *in vivo*, and the level of inhibition of transcription that would correlate with inhibition of proliferation, the skilled artisan would not have had a reasonable expectation of success in selectively inhibiting the proliferation of hematopoietic cells *in vivo* using the instant invention.

The specification does not provide an enabling disclosure for the selective inhibition of proliferation of transplanted hematopoietic cells or the treatment of graft-versus-host disease in an individual comprising transplanting hematopoietic cells of which a sub-population express a

mutated MBP, followed by administration of a complementary macrolide analog. Graft-versus-host disease (GVHD) is caused by the activation of transplanted allogeneic or xenogeneic immune effector cells, primarily T cells, by the endogenous antigens of the host mammal. As a preferred embodiment of the invention, the specification discloses that the T cells of the transplanted hematopoietic cells will be selectively targeted for inhibition by either targeted transfection with a mutated MBP construct, or by the use of a T cell specific promoter, thereby providing a means to inactivate the cells which are primarily responsible for GVHD. However, the specification does not provide guidance as to the percentage of T cells which need to be transfected, or the level of expression of the mutated MBP in the donor T cells that is required to treat GVHD. In addition, the specification discloses that the transient expression of the mutated MBP may be sufficient to tolerize the donor T cells, thereby preventing GVHD after administration of the macrolide analog is discontinued. In a review of GVHD prevention, Blazar et al. teach that, "despite high doses of FK506, donor T cells continued to persist > 100 days post-BMT in numbers exceeding those originally infused on day 0 post BMT, suggesting expansion", and that, " it would be predicted that mature T cells escaping FK506 would not be rendered tolerant of host alloantigens. In that event, T cells escaping FK506-mediated inhibition could receive sufficient T-cell signaling to become primed to host alloantigen and mediate GVHD, especially once FK506 was discontinued" (Blazar et al. (1997), Immunological Reviews, Vol. 157, page 86, column 1, paragraph 2, and column 2, paragraphs 1-2). Thus, the percentage of donor T cells expressing the mutated MBP would be critical to the success of the instant invention, and in the absence of guidance from the

specification, the skilled artisan would not predict that GVHD could be treated when expression of the mutated MBP was transient and where the percentage of donor T cells expressing the mutated MBP was less than 100%.

The term "treatment" covers a wide range of clinical outcomes, from disease prevention to cure of pre-existing disease. The specification does not provide guidance for the prevention or cure of acute or chronic GVHD. It does not provide guidance as to the amount of time between administration of the transfected donor cells and the administration of the macrolide analog, or the route, dosage, and frequency of administration of the macrolide analog. At the time of filing, no pharmacological treatment was recognized as capable of completely preventing or curing GVHD: even combination therapy using a macrolide such as cyclosporin or FK506 and prednisone or methotrexate can only decrease the incidence and severity of GVHD (Bron et al. (1994) Curr. Opin. Oncol., BOl. 6, page 358, abstract and paragraph 1, and Hertenstein et al. (1998) BioDrugs, Vol. 9 (2), page 105, paragraph 1). Thus, due to the lack of guidance for the parameters listed above, the state of the art of GVHD therapy at the time of filing, the breadth of the claims, and in the absence of evidence to the contrary, the skilled artisan would not have had a reasonable expectation of success in treating GVHD in a patient using the instant invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear from the phrase " at least a sub-population of hematopoietic cells" what the characteristics of the sub-population of cells might be and what percentage of these cells need to be transduced in order for graft-versus-host disease to be treated.

Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The method for treating graft-versus-host disease (GVHD) does not relate the inhibition of proliferation of a sub-population of hematopoietic cells with the treatment of GVHD.

The claims are free of the prior art since the literature at the time of filing did not teach the combination of a mutated macrolide binding protein and a mutated macrolide capable of binding one to the other that retained the capacity to inhibit the calcineurin - NFAT pathway, nor the use of the mutated macrolide for selectively inhibiting proliferation of cells expressing the mutated macrolide binding protein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-

9156. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

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Dr. A.M.S. Beckerleg

October 30, 1998